Amendments to the Specification:

Please replace paragraph beginning on page 6, line 1 with the following amended paragraph:

FIGS. 5A-5E show[[s]] the full length amino acid sequence of ß-secretase 1-501 (SEQ ID NO: 2), including the ORF which encodes it (SEQ ID NO: 1), with certain features indicated, such as "active-D" sites indicating the aspartic acid active catalytic sites, the transmembrane region commencing at position 453, as well as leader sequence (1-22; SEQ ID NO: 46) and putative pre-pro region (23-45; SEQ ID NO: 47) and where the polynucleotide region corresponding the proenzyme region (nt 135-1503) represents SEQ ID NO: 44.

Please replace paragraph beginning on page 6, line 18 with the following amended paragraph:

FIGS. 10A-10D shows an alignment of the amino acid sequence of human ß-secretase ("Human Imapain.seq")(SEQ ID NO:65) compared to various mouse constructs(SEQ ID NOS:81-84), with the lowest construct in each row ("pBS/mImpain H#3 cons")(SEQ ID NO:85) representing a consensus mouse sequence~~: SEQ ID NO: 65~~.

Please replace paragraph beginning on page 6, line 1 with the following amended paragraph:

FIGS. ~~13(A-E) shows~~ 13A-13W show the nucleotide sequence of pCEK clone 27 (SEQ ID NO: 49), with the OFR indicated by the amino acid sequence SEQ ID NO: 2.

Please replace Table 3 beginning on page 27, line 28 with the following amended paragraph:

Table 3

N-terminal Sequences and Amounts of ß-secretase Forms in Various Cell Types

Source	Est. Amount (pmoles)	N-terminus (Ref.: SEQ ID NO: 2)	Sequence
Human brain	1-2	46	ETDEEPEEPGR... (SEQ ID NO: [[76]]88)
Recombinant, 293T	~35	46	ETDEEPEEPGR... (SEQ ID NO:[[76]]88)
	~7	22	TQHGIRL(P)LR... (SEQ ID

	~5	63	NO:[[77]]89) MVDNLRGKS... (SEQ ID NO:[[78]]90)
Recombinant, CosA2	~4	46	ETDEEPEEPGR... (SEQ ID NO:[[76]]88)
	~3	58	GSFVEMVDNL... (SEQ ID NO:[[79]]91)

Please replace paragraph beginning on page 51, line 24 with the following amended paragraph:

It was found that the P1 site is quite sensitive to substitution for binding with only Leu (the Swedish mutation substitution) and Phe showing appreciable cleavage (30%). Next P1 was allowed to remain as Leu and P1' was varied by substitution with different amino acids. Interestingly, when P1' was varied there was quite a range of enzyme activity but when P1' was valine, the reaction kinetics showed that the enzyme became fully saturated. Thus this valine variant had good binding affinity for the protein as well as slowing the rate of cleavage of the bound complex.. An IC50 value of the 18 residue sequence in an MBP M125 assay was measured as 3 μM, ~~3 μm,~~ which indicated an enzyme inhibition of over 100 times that of the Swedish sequence. This result demonstrated a clear effect on enzyme turnover. As a result, valine was selected as the amino acid substitution at P1' with further variation of P1 and more remote binding sides to be studied. When statine a non-standard amino acid known to inhibit renin, another aspartyl protease, was substituted at P1 with P1' being valine, a potent inhibitor of ß-secretase was created. The P10-P4'sta D→V inhibitor discussed above also incorporates this P1-Pi' sequence and is about 100 times more potent an inhibitor than the valine substitution alone.

Please replace paragraph beginning on page 63, line 18 with the following amended paragraph:

Poly A+ RNA from IMR human neuroblastoma cells was reverse transcribed using the Perkin-Elmer kit. Eight degenerate primer pools, each 8 fold degenerate, encoding the N and C

terminal portions of the amino acid sequence obtained from the purified protein were designed (shown in Table 6; oligos 3407 through 3422). PCR reactions were composed of cDNA from 10 ng of RNA, 1.5 mM $MgCl_2$, 0.125 µl AmpliTaq® Gold, 160 µM each dNTP (plus 20µM additional from the reverse transcriptase reaction), Perkin-Elmer TAQ buffer (from AmpliTaq® Gold kit, Perkin-Elmer, Foster City, CA), in a 25 µl reaction volume. Each of oligonucleotide primers 3407 through 3414 was used in combination with each of oligos 3415 through 3422 for a total for 64 reactions. Reactions were run on the Perkin-Elmer 7700 Sequence Detection machine under the following conditions: 10 min at 95°C, 4 cycles of, 45° C annealing for 15 second, 72° C extension for 45 second and 95°C denaturation for 15 seconds followed by 35 cycles under the same conditions with the exception that the annealing temperature was raised to 55° C . (The foregoing conditions are referred to herein as "Reaction 1 conditions.") PCR products were visualized on 4% agarose gel (Northern blots) and a prominent band of the expected size (68 bp) was seen in reactions, particularly with the primers 3515-3518 in many of the lanes (each of FIGS 3A-3C shows two gels, an upper and a lower gel, and the reaction combinations were run sequentially in the gels as illustrated, such that primer 3515 was reacted with each of 3507-3514, followed by reaction of primer 3516 with each of primers 3507-3514, and so forth). The 68 kb band was sequenced and the internal region coded for the expected amino acid sequence. This gave the exact DNA sequence for 22 bp of the internal region of this fragment. C.GGC.CGG.AGG.GGC.AGC.TTT.GTG (SEQ ID NO:[[81]]101)

Please replace paragraph beginning on page 66, line 8 with the following amended paragraph:

Clones from the 1.5 kb pool were screened using a radiolabeled probe generated from a 390 b.p. PCR product generated from clone 9C7E.35. For generation of a probe, PCR product was generated using 3458 and 3468 as primers and clone 9C7E.35 (30 ng) as substrate.

3468: CAG.CAT.AGG.CCA.GCC.CCA.GGA.TGC.CT (SEQ ID NO:[[82]]20)

3458: GAG GGG CAG CTT TGT GGA GA (SEQ ID NO:[[83]]19)

Please replace paragraph beginning on page 73, line 10 with the following amended paragraph:

Recombinant proteins were generated with both the wild-type APP sequence (MBP-C125 WT) at the cleavage site (..Val-Lys-Met-Asp-Ala..)(SEQ ID NO:[[84]]54) or the "Swedish" double mutation (MBP-C125 SW) (..Val-Asn-Leu-Asp-Ala..)(SEQ ID NO:[[85]]51). As shown in FIG. 19, cleavage of the intact MBP-fusion protein results in the generation of a truncated amino-terminal fragment, with the new SW-192 Ab-positive epitope uncovered at the carboxy terminus. This amino-terminal fragment can be recognized on Western blots with the same Ab, or, quantitatively, using an anti-MBP capture-biotinylated SW-192 reporter sandwich format, as shown in FIG. 19.

Please replace paragraph beginning on page 82, line 5 with the following amended paragraph:

After the sequential addition of all fourteen residues the P10-P4'sta(D->V) peptide has the sequence NH_2-KTEEISEVN[sta]VAEF-COOH (SEQ ID NO:[[86]]72), where "sta" represents a statine moiety. The side chain protected peptide resin was deprotected and cleaved from the resin by reacting with anhydrous hydrogen fluoride (HF) at 0°C for one hour. This generated the fully deprotected crude peptide as a C-terminal carboxylic acid.

Please replace Table 9, beginning on page 83 with the following amended table:

Table 9

Example	P5		P3		P1	P1			P4	P5	IC_{50} Group
(Swedish) SEQ ID NO:92	S	E	V	N	L	D	A	E	F	R	
7B			|AcV-	--M--	-Sta--	--V---	------	------	------|		I
7C			|-----	------	------	-Abu-	------	------	------|		II
7D			|-----	------	------	-Phg-	------	------	------|		II
7E			|-----	------	------	--A---	------	------	------|		II
7F			|-----	------	------	t-Leu	------	------	------|		IV
7G			|-----	-Phg-	------	--V---	------	------	------|		I

7H			|-----	n-Leu	------	------	------	------	------|		I
7I			|-----	--N--	------	------	------	------	------|		II
7J			|-----	--F--	------	------	------	------	------|		II
7K			|-----	--E--	------	------	------	------	------|		II
7L			|-----	--V--	------	------	------	------	------|		IV
7M			|-----	--G--	------	------	------	------	------|		II
7N			|-----	--M--	------	xxxx†	-------	------	------|		II
70			|-----	------	phe-Sta	--V---	-------	------	------|		I
7P			|-----	------	nor-Sta	-------	-------	------	------|		II
7Q			|(NH_2)	------	acha	-------	-------	------	------|		II
7R			|-----	------	-Sta--	-------	xxxx	------	------|		II

Please add the paper copy of the second substitute sequence listing enclosed in the Appendix to the application.